DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

Dallas District
4040 North Central Expressway
Dallas, Texas 75204-3145

July 17, 2003

Ref: 2003-DAL-WL-14

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Norman Kalmin, M.D.
President, CEO, and Medical Director
South Texas Blood and Tissue Center
6211 IH-10 West
San Antonio, TX 78201

Dear Dr. Kalmin:

The Food and Drug Administration (FDA) conducted an inspection of South Texas Blood and Tissue Center located in San Antonio, Texas (hereinafter, "your facility"), from February 24 through March 18, 2003. During the inspection, the FDA investigators documented violations of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) and Title 21, Code of Federal Regulations [21 CFR] Part 211 and Parts 600-680. Listed below are certain serious violations that reveal problems with your facility's quality assurance and oversight functions; we did not list all of your facility's violations. These violations represent both observations noted on the Form FDA-483 issued at the conclusion of the inspection as well as additional issues identified upon review of information that the investigators collected during the inspection:

1. Your facility failed to follow the manufacturer's instructions, as well as your facility's own written standard operating procedures (SOPs), when performing screening tests and repeat tests on blood and blood components [21 CFR 610.40(b), 606.100(b)(7), and 211.100(b)]. For example,

    a. Your facility's SOP PL02.0402, entitled "[redacted]HIVAB HIV-1/HIV-2 (rDNA) EIA, contains instructions, consistent with the manufacturer's instructions, to retest initially reactive samples in [redacted]. If either [redacted]test is reactive, the sample must be

interpreted as repeatedly reactive for the antibodies to the human immunodeficiency virus ("HIVAB").

We understand that your facility has dedicated particular [redacted] instruments for testing either whole blood or source plasma, but that those instruments are capable of testing both whole blood and source plasma. That arrangement is acceptable, as long as your facility maintains proper controls.

Our inspection disclosed that on September 7, 2002, your facility performed the initial testing on Source Plasma unit [redacted] which another blood manufacturer had collected, and that the unit tested initially reactive for HIVAB. On September 9, 2002, your facility retested Source Plasma unit [redacted] using the [redacted] dedicated for whole blood because the instrument dedicated for source plasma testing was not available at that time. The unit tested repeatedly reactive for HIVAB. Based on that test result, your facility reported to the blood manufacturer who had collected the unit that it tested positive for HIVAB. According to your facility's SOP and the [redacted] manufacturer's instructions, your facility should have accepted that test result as final.

Nevertheless, on September 12, 2002, your facility retested Source Plasma unit STO828555 a second time using the [redacted] dedicated to testing source plasma. The unit tested repeat negative. Based on these subsequent duplicate-repeat test results, your facility sent a second report to the blood manufacturer that had collected the unit, this time stating that the unit is negative.

2. Your facility failed to follow established procedures applicable to the quality control unit [21 CFR 211.22(d)]. For example,

   a. According to SOP QA01.0020, entitled "Quality Plan," management review of quality assurance information is supposed to take place through the Quality Review Board (QRB). The QRB must review customer complaints, Quality Improvement Reports (QIRs), quality indicators, Corrective Action Reports (CARs), and internal audit reports. The QRB has responsibility for determining the relevant action, such as initiating additional internal audits, changing or adding quality indicators, and/or forming task force teams for additional data collection, when necessary.

      i. For the time period of May 13, 2002 to March 1, 2003, your facility documented approximately 2,330 QIRs. One hundred

eighty-seven (187) of the 2,330 QIRs pertained to improper donor screening. The root cause was attributed to screener error, yet no investigation was performed as to why these errors continued to occur. The QRB failed to trend or evaluate these violations or to direct others to do so. During a QRB meeting in which the QRB discussed QIRs pertaining to these events, the QRB cursorily concluded that "this issue will be resolved once [redacted] is implemented." We saw no evidence that the QRB determined how the anticipated [redacted] would address these donor screening errors or when your facility will implement this system. Additionally, the QRB failed to identify or implement any corrective or preventive action plan in the interim.

ii. For the months of December 2002 and January 2003, the QRB issued 13 Process Change Requests (PCRs), which are used for planning and controlling the design and development of a product/process. According to documentation from quality assurance meetings, the QRB assigned employees to implement only 5 of those PCRs. And even on those 5, we received no evidence that the QRB evaluated the results of the follow-up action it directed.

iii. For the time period between May 2002 and March 2003, your facility failed to submit 48 out of 155 (31%) of Biological Product Deviation Reports within the 45-calendar days required in 21 CFR 606.171(c). Your facility failed to take corrective or preventive actions for this frequent reporting delay, and failed to determine a root cause for the recurrence of this repeated deviation.

b. According to SOP QA01.0020, entitled "Quality Plan," the QRB must meet [redacted] to review collected and trended quality data for possible preventative actions.

i. During the 4 month period between September and December 2002, QRB meeting minutes indicate that the QRB met only once.

c. According to SOP QA09.0061, entitled "Preventive Action Plan," the QRB must request preventive action when action is required to prevent the occurrence of nonconformities and must address Preventive Action Requests ("PARs") to the responsible party. The responsible party must determine the appropriate preventive action and must summarize actions taken on a designated form.

i. Between May 2002 and March 2003, your facility generated approximately 2,330 QIRs, which documented various nonconformities, including improper donor screening, improper testing, improper component handling, incorrect procedures, and improper application of procedures. During this same time period, the QRB requested only 1 PAR, which was to address a problem with clotting. No PAR's were generated to address how to correct and prevent all the other non-conformities.

3. Your facility failed to check input to and output from its computer and related systems for accuracy [21 CFR 211.68(b)]. For example,

   a. Your facility's [redacted] computer system and [redacted] lacked controls or procedures to prevent improper sample analysis or mix-ups. As explained above (1.a), your facility retested a unit of source plasma in [redacted] two separate times, on two different days using two different instruments, and obtained opposite results. Your facility reported both discrepant results to the blood manufacturer that had collected the unit. Your facility should have established controls to ensure that one unit would not be retested in duplicate more than once, and to ensure that your facility would not report discrepant testing results to a manufacturer.

   b. Your facility did not evaluate the [redacted] computer system to assure its proper performance before your facility implemented that system in 2001. Until November 2002, your facility used that system during the donor deferral process to verify medications that affect blood collection. When too many personnel use this system, it converts to a status that renders it inoperable. As a result, your facility had to conduct 4 recalls between July 2002 and October 2002 for donors who were improperly accepted for donation due to their medication status because this instrument malfunctioned.

The above-identified deviations are not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility as CEO to assure that your establishment is in compliance with all requirements of the federal regulations. You should take prompt measures to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. Such action includes license suspension and/or revocation, seizure and/or injunction.

We received your May 13, 2003 response, to the Form FDA-483 that the FDA investigator issued at the conclusion of the most recent inspection of your facility. We have completed our review of your response and have determined that your response is inadequate to address all the violations that FDA documented at your firm. Our evaluation of your response follows and is numbered or labeled to correspond to the items as they appeared on the Form FDA-483 and in your response:

Items 1, 2, 6.a.1, and 8:
We have determined that the response is inadequate to address the noted observations. The response stated that procedures have been implemented requiring that the source plasma-dedicated [redacted] equipment be used exclusively for testing source plasma collections. Your facility's procedures had already required use of dedicated testing equipment for whole blood and source plasma collections. However, staff were able to circumvent the procedures, resulting in the use of non-dedicated [redacted] equipment in testing of whole blood and source plasma samples. The proposed corrective action does not provide further assurance that the problem will not recur, or that the proposed procedures eliminate the potential that similar testing errors might recur.

Items 3, 4, and 6.b.2:
The response appears adequate to address the noted observations. However, the response stated that "...Management was called to determine eligibility, but were not given enough information to accurately assess the situation." It appears that the staff followed procedures by referring events, in which they could not adequately determine donor suitability, to management. In several instances, management determined that the donors were suitable for donation. It was noted in the investigation of the events that the corrective action was to re-train the staff. However, management who were involved in the incidents were not re-trained. We believe that the donor suitability deviations appear to be attributed to errors in management's assessments of the events and their failure to gather enough information to properly assess the donor for donation.

Item 5:
The response appears adequate to address the noted observation.

Items 6.a.1-5, and 10:
Please refer to our comments under the general response section below concerning quality assurance issues.

Items 6b, 7b, 7c, and Item 9:
You stated in your response that "The manual thermometer used to check questionable temperatures has been replaced with a faster, easy to use

digital thermometer." We remind you that maintenance, calibration, inspection, and qualification of the digital thermometer, as with all equipment used in the manufacture, processing, packing and holding of a drug product, should be performed pursuant to the applicable federal regulations.

Item 6c:
The proposed corrective action in the response appears adequate to address the noted observation.

Item 6d:
The proposed corrective action in the response appears adequate to address the noted observation.

Item 6e:
The proposed corrective action in the response appears adequate to address the noted observation.

Discussion item 1:
We have determined that the response is inadequate to address the noted item. 21 CFR 606.171 outlines the requirements for Biological Product Deviation Reporting. Blood establishments are required to comply with the BPDR regulations regardless of any extraordinary, unexpected, or additional events that may concurrently occur. Your practices and/or views regarding BPDRs do not comply with the applicable regulations.

Discussion item 2:
The proposed corrective action in the response appears adequate to address the noted discussion item.

Discussion item 3:
The proposed corrective action in the response appears adequate to address the noted observation.

Additional Comments to General Response and to Discussion Items:

In your response, you stated that "This information is reviewed by the Quality Review Board. Based on this review, the board can request preventive or corrective action." We have determined that this response is inadequate. Significant problems exist in your firm's Quality Assurance system and are related to a failure to follow established procedures that are applicable to the quality control unit. These problems are referenced in paragraph 2 of this Warning Letter.

CP02.0952 Documentation of Nonconforming Blood Components: This procedure includes 2 appendices. Appendix B, which is a 1-page reference, is an abbreviated list of nonconformant product reject codes taken from Appendix A, which is a 3-page reference of all nonconformant product reject codes. Appendix B is redundant, unnecessary, and increases the likelihood of miscoding nonconformant product. There is the question of whether both appendices are available as a ready reference to personnel. If so, all reject codes in Appendix B are also incorporated into Appendix A, so there is no need for Appendix B. If only Appendix B is available as a ready reference, then the additional product reject codes found only in Appendix A will not be used. There does not seem to be any need or enhanced value to Appendix B since it is only an abbreviated list taken from Appendix A and is therefore a duplicative reference. For these reasons, Appendix B should be removed from the procedure, CP02.0952.

Please notify this office in writing, within 15 working days of receipt of this letter, of the additional steps you have taken to correct the noted violations and to prevent their recurrence. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

Your reply should be sent to the Food and Drug Administration, Dallas District Office, Attention: Brenda C. Baumert, Compliance Officer, at the above letterhead address.

Sincerely yours,

Michael A. Chappell,
Dallas District Director